CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125284/0
Product: Antithrombin alfa
Sponsor: GTC Biotherapeutics
Indication: For the prevention and treatment of thromboembolic events
Date Received: August 8, 2008
Reviewer: Iftekhar Mahmood, Ph. D.
RPM: Pratibha Rana
Through: Basil Golding, M.D.

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INTRODUCTION

Antithrombin (AT) deficiency is a more severe disorder than other inherited thrombophilias. Around 50% of individuals heterozygous for antithrombin deficiency develop venous thrombosis and suffer with major venous thromboembolism at a younger age than those with other thrombophilic abnormalities. Antithrombin deficiency is associated with a high risk of venous thrombosis complicating surgery or childbirth. Recombinant human AT (rhAT) with or without

concomitant heparin depending on the individual patient and situation offers safe and efficacious thromboprophylaxis for the AT deficient patients.

Reduced plasma antithrombin activity causes heparin to be relatively ineffective. Because of the high risk of venous thromboembolism associated with surgery or delivery, supplementation of endogenous antithrombin activity with antithrombin concentrates has been recommended and widely used in these situations in patients with inherited antithrombin deficiency. In patients with congenital antithrombin deficiency, intravenous administration of recombinant human AT (rhAT), raises plasma antithrombin activity and with therapeutic monitoring and dose adjustment after a calculated loading dose, plasma antithrombin activity can be maintained between 80% and 120% of normal with continuous intravenous infusion of rhAT.

The use of human plasma derived AT (hpAT) is well established in congenital AT deficient patients in high-risk situations. RhAT is a highly purified, well-characterized glycoprotein and has been shown to be structurally identical to hpAT except for differences in glycosylation. The pharmacodynamic actions of rhAT are also very similar to hpAT.

The sponsor has submitted four pharmacokinetic studies in this Biologic license Application (BLA). The review of these studies can be found on pages 6-16.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.3 Pharmacokinetics

~~After intravenous bolus dose of 50 IU/kg or 100 IU/kg body weight of ATryn to hereditary antithrombin deficient patients without clinical symptoms of thrombosis, not in high-risk situations and not using heparin, the incremental recovery was 2.07 ± 1.54 %/IU/kg body weight (mean ± SD). The pharmacokinetic parameters for ATryn derived from the same study revealed (mean ± SD): are summarized in the following Table.~~

In an open-label, single dose pharmacokinetic study, male and female patients (≥ 18 years of age) with hereditary AT III deficiency, received either 50 (n = 9 all females) or 100 (n = 5, 2 males and 3 females) IU/kg rhAT III intravenously. These patients were without clinical symptoms of thrombosis, were not in high-risk situations and were not using heparin. The baseline corrected pharmacokinetic parameters for rhAT III (ATryn) are summarized in the following Table.

Table: Mean (%CV) pharmacokinetic parameters for ATryn

Parameters	Baseline corrected (n = 9)	
	50 IU/kg	100 IU/kg
CL (mL/hr/kg)	9.6 (34.4)	7.2 (15.3)
Half-life (hrs)	11.6 (84.7)	17.7 (60.9)
MRT (hrs)	16.2 (74.9)	20.5 (40.2)
V_{ss} (mL/kg)	126.2 (37.4)	156.1 (43.4)

The incremental recovery was 2.07 ± 1.54 %/IU/kg body weight.

~~• Area under the curve: 587.88 ± 1.63 (% x h)~~
~~• Distribution half-life: 1.74 ± 1.28 h, elimination half-life: 10.16 ± 1.28 h~~
~~• Mean residence time (MRT): 8.57 ± 1.24 h~~
~~• Clearance: 0.665 ± 0.0493 L/h (Mean ± SE)~~

~~Clearance and volume of distribution are significantly increased in pregnant patients as compared to non-pregnant patients. Therefore, distinct dosing formulae for surgical and pregnant patients should be used (see 2.1, Dosage and Administration, Hereditary Antithrombin Deficiency).~~

The above statement was deleted because the population pharmacokinetic model developed from non-pregnant patients over-predicted the clearance and volume of distribution in pregnant patients compared to observed values in this population.

Sponsor: Please modify your statement as follows:

The clearance and volume of distribution in pregnant patients were (sponsor: please fill in the observed values) which are higher than non-pregnant patients (sponsor: please fill in the observed values). Therefore, distinct dosing formulae for surgical and pregnant patients should be used (see 2.1, Dosage and Administration, Hereditary Antithrombin Deficiency).

Pharmacokinetics may be influenced by concomitant heparin administration, as well as surgical procedures, delivery, or bleeding. Therapeutic drug monitoring (see 2.1, Dosage and Administration, Hereditary Antithrombin Deficiency) should be performed to properly treat such patients.

RECOMMENDATION

The pharmacokinetic study design and analysis of rhAT III is acceptable. The sponsor should incorporate the clinical pharmacology labeling of rhAT III as suggested by the FDA.

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Study #1

Title: A phase I, randomized, placebo controlled study to evaluate the safety, tolerance, pharmacokinetics and pharmacodynamics to transgenically derived antithrombin III (tg AT III) when given intravenously as single, ascending doses to normal healthy male subjects (GEN/G 9601).

This was a phase I, randomized controlled study. There were 20 healthy Caucasian male subjects (19-29 years of age). The subjects were divided into five groups of four. In each group, 3 subjects received active drug and one subject received a saline placebo. The subjects received 10 to 200 IU/kg of tg AT III as IV infusion over 30 minutes. Blood samples were taken at baseline, 15 minutes from start of infusion, at the end of the infusion, then at 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 36 hours. Blood samples to measure antibodies to tgAT III were obtained at baseline and at days 7 and 28 following drug administration.

AT-III concentrations, relative to a reference standard, were measured in a ---b(4)---------- ---------- assay. The measured concentrations reflect the sum of endogenous AT-III plus tgAT-III. Since AT-III measurements in control subjects differed from each other by as much as 0.37 IU/mL, tgAT III values that were close to 0.4 IU/mL were considered too close to the background values and were used as lower limit of detection. Plasma concentrations of AT III were expressed as percentage of a human plasma reference standard. The concentration of AT III in this reference standard was assigned a value if 1 IU/mL. Total AT III values (IU/mL) were calculated by multiplying the percentage reported by a factor 0.01. The final concentrations of AT III (IU/mL), for each time point, were calculated by subtracting, the pre-dose value of AT III (IU/mL) for that subject.

Model independent (non-compartmental) approach was used to calculate baseline corrected PK parameters (summarized in Table 1). AT III concentrations were back to the baseline 12 hours after the drug administration. The pharmacokinetics of 10 IU/kg could not be estimated because the blood levels were below <0.4 IU/mL (lower limit of detection).

TABLE 1
Pharmacokinetic parameters ((mean (%CV)) of AT III in healthy subjects

Parameters	Mean (n = 3)			
Intended dose (IU/kg)	50	100	150	200
Actual dose (IU/kg)	43	86	129	171
$AUC_{(0\text{-}inf)}$ (IU*hr/mL)	4.4 (34)	14.2 (22)	22.1 (8)	30.1 (13)
Clearance (mL/hr/kg)	10.3 (28)	6.2 (19)	5.9 (8)	5.7 (14)
Half-life (hrs)	2.6 (31)	4.4 (16)	4.8 (15)	4.3 (9)
V_{ss} (mL/kg)	39.9 (4)	41.1 (14)	41.2 (10)	36.2 (7)
MRT (hrs)	4.1 (29)	6.7 (16)	7.0 (14)	6.3 (10)

AT III appears to follow linear kinetics from 86 to 171 IU/kg dose. The PK parameters following the 50 IU/kg dose appears to be outlier. This is probably because the assay is less sensitive at low concentrations of AT III. The half-life ranged from 2.6 to 4.8 hours across doses. There were no indications of subject's immune response in any of the dosing cohorts.

Conclusions: Overall, the pharmacokinetic results of rhAT III in healthy subjects indicate a short half-life and exhibit linearity over the dose range of 86 to 171 IU/kg but if studied may be linear even over a wider dose range.

Study #2

Title: A single-dose pharmacokinetic study of rhAT III in patients with hereditary AT III deficiency (Protocol # AT III-009-00).

This was an open-label, single dose pharmacokinetic study in male and female patients (≥ 18 years of age) with hereditary AT III deficiency. The patients received either 50 (n = 9 all females) or 100 (n = 6, 2 males and 4 females) IU/kg rhAT III intravenously (bolus). Three different lots of rhAT III were used and 5 patients received dosing from each lot. Blood samples were collected before the administration of the drug and at 5, 10, 15, 30, 45, and 60 minutes and at 2, 4, 6, 8, 24, 48, and 72 hours. Plasma concentrations (measured as percent activity) of rhAT III were measured by a --b(4)--- kit. Blood samples were also collected at day 28 and day 60 for antibody measurement (----------b(4)-------- assay). The pharmacokinetic parameters were estimated with and without baseline correction for rhAT III activity. Incremental recovery expressed as (rise in IU/mL divided by IU/kg infused) was calculated as follows:
Incremental recovery = (C_{max} within one hour from end of infusion – average baseline) divided by dose in IU/kg.

Baseline corrected PK of rhAT III:

Tables 1 summarize the baseline corrected pharmacokinetic parameters of rh AT III.

TABLE 1

Baseline corrected mean pharmacokinetic parameters for rhAT III.

		rh AT III 50 IU/kg			rh AT III 100 IU/kg		
	Units	N	Mean	%CV	N	Mean	%CV
$AUC_{0\text{-}inf}$	%^{x}h	9	595.5	44.50	5	1413.8	15.59
$AUC_{0\text{-}t}$	%^{x}h	9	539.4	38.47	5	1289.8	16.31
CL	mL/hr/kg	9	9.6	34.44	5	7.2	15.29
C_{max}	%	9	112.0	20.21	5	193.8	14.81
$t_{½}$	Hr	9	11.6	84.70	6	17.7	60.91
K_{el}	1/hr	9	0.0884	54.80	6	0.0512	47.69
MRT	Hr	9	16.2	74.90	5	20.5	40.25
T_{max}*	Hr	9	0.22	(0.13-0.45)	5	0.25	(0.17-0.33)
Vd/F	mL/kg	9	132.5	47.45	5	192.2	50.28

*Median and range are displayed for T_{max}.

The mean baseline rh AT III plasma concentration in units of percent activity for 50 IU/kg and 100 IU/kg was 52 (range = 51.2 to 52.6) and 48.6 (range = 47.8 to 49.3), respectively. With the corrected baseline, the C_{max} and AUC appear to increase proportionally with dose. However, with only two doses it is difficult to assess the dose linearity. The clearance and half-life of rhAT III were 9.6 and 7.2 mL/hr/kg and 11.6 and 17.7 hours following 50 and 100 IU/kg dose,

respectively. In Table 3 and Figure 1, baseline corrected mean concentrations of rhAT III against time are presented.

Baseline un-corrected PK of rhAT III:

Tables 2 summarize the baseline un-corrected pharmacokinetic parameters of rh AT III. As compared to baseline corrected C_{max} and AUC, uncorrected baseline C_{max} and AUC did not increase proportionally with dose. In Table 4 and Figure 2, baseline un-corrected mean concentrations of rhAT III against time are presented.

TABLE 2

Baseline un-corrected mean pharmacokinetic parameters for rhAT III.

		rh AT III 50 IU/kg			rh AT III 100 IU/kg		
	Units	N	Mean	%CV	N	Mean	%CV
AUC_{0-t}	%^{x}h	9	4334.4	10.66	5	4825.7	7.89
C_{max}	%	9	163.9	14.10	5	242.8	12.71
T_{max}*	h	9	0.23	(0.13-0.45)	5	0.24	(0.17-0.33)
INREC		9	2.24	20.21	5	1.94	14.81

*Median and range are displayed for T_{max}.
INREC = incremental recovery

TABLE 3

Baseline corrected mean concentrations of rhAT III

Blood Sampling Time (h)	rh AT III 50 IU/kg		rh AT III 100 IU/kg	
	Mean	%CV	Mean	%CV
0.00	108.8	21.90	189.3	14.94
0.08	109.7	21.12	191.4	13.46
0.17	105.6	17.22	192.0	18.56
0.25	97.5	21.25	184.8	18.12
0.50	93.0	22.09	177.8	18.01
0.75	82.8	21.82	164.2	16.70
1.00	76.1	21.52	160.0	18.77
2.00	51.4	20.02	122.4	21.86
4.00	27.6	24.23	68.4	29.57
6.00	16.5	20.97	45.6	19.05
8.00	12.7	36.42	31.7	28.58
24.00	4.0	70.93	8.9	25.84
48.00	2.0	164.80	2.8	67.28
72.00	1.5	122.30	3.7	74.37

Figure 1. rhAT III mean baseline corrected plasma activity profiles (linear scale)

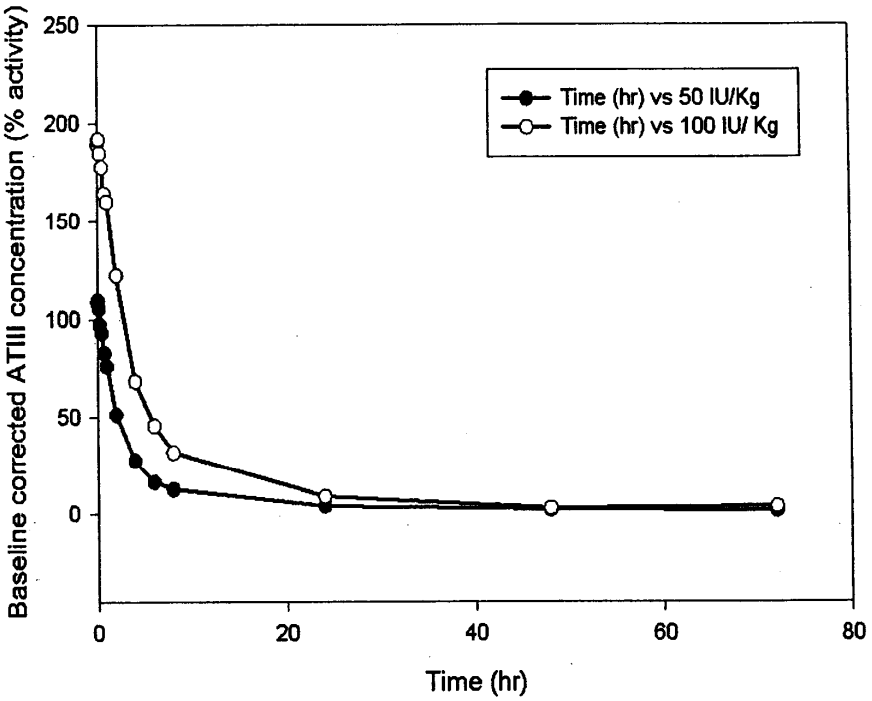

Figure 2. rhAT III mean baseline uncorrected plasma activity profiles (linear scale)

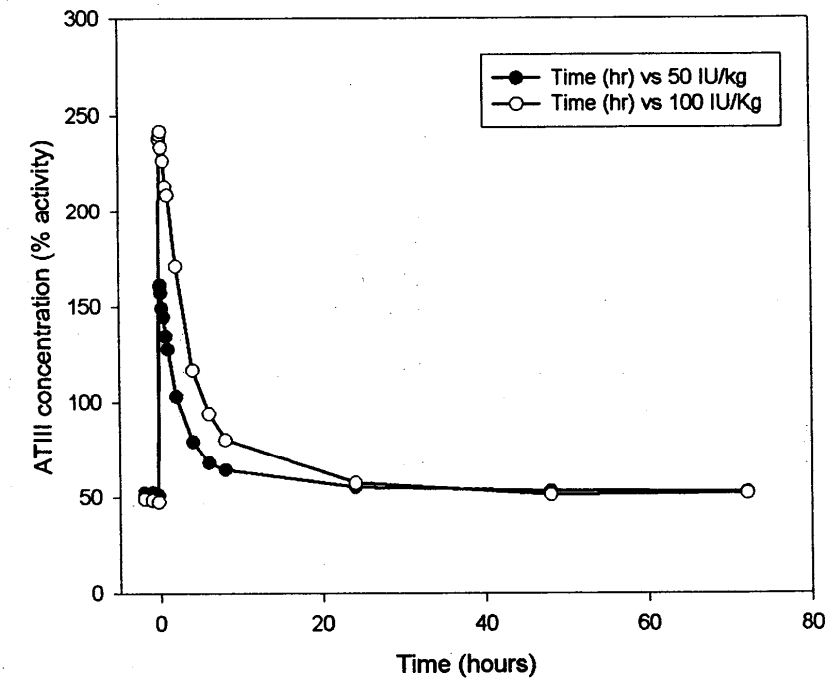

TABLE 4

Baseline un-corrected mean concentrations of rhAT III

Blood Sampling Time (h)	rh AT III 50 IU/kg n=9		rh AT III 100 IU/kg n=6	
	Mean	%CV	Mean	%CV
Screening	52.4	8.04	49.3	5.23
-1.00	52.6†	12.60	48.7*	8.49
-0.25	51.2	11.08	47.8*	7.76
0.00	161.1†	14.43	238.0*†	13.07
0.08	161.6	14.36	240.4*	11.64
0.17	157.4	12.07	242.0*†	15.54
0.25	149.3	14.39	233.8*	15.12
0.50	144.9	13.83	226.8*	15.00
0.75	134.7	14.15	213.2*	13.92
1.00	128.0	13.45	209.0*	15.36
2.00	103.2	11.47	171.4*	16.74
4.00	79.4	9.95	117.0	19.10
6.00	68.3	8.31	94.2	10.90
8.00	64.6	11.15	80.3	13.21
24.00	55.4	12.69	57.5	5.01
48.00	53.4	13.97	51.3	8.05
72.00	52.7	12.88	52.2	10.80

*n = 5 for time points 0.08, 0.25, 0.50, 0.75, 1.00, 2.00 hour due to lack of sufficient sample to assay for Patient 120212

†These time points missing values from patients as they were not provided in the original data.

Comments

The clearance and half-life values of rhAT III in patients with hereditary AT III deficiency appear to be different than the healthy volunteers. There may be several reasons for this discrepancy and are summarized below:

1. For healthy subjects, blood samples were taken till 36 hours whereas for patients the blood samples were collected till 72 hours. In healthy subjects and patient population, the rhAT III activity returned to the baseline by 12 and 24 hours, respectively The half-life of rhAT III in healthy subjects was calculated using data till 12 hours (baseline corrected) whereas half-life in patients was calculated using data till 72 hours (baseline corrected). In healthy subjects, due to high baseline values, it was not possible to have rhAT III concentrations beyond 12 hours (in most of the subjects). On the other hand, in the patients, baseline values were about 50% of the healthy subjects and therefore, it was

possible to have measurable concentrations (above baseline) till 24 hours. In some subjects, the measurable concentrations were till 72 hours which resulted in a longer half-life than most of the other patients. Therefore, overall mean half-life in patients is higher than healthy subjects.

2. The baseline uncorrected AUC is considerably higher than the baseline corrected AUC because the contribution to the total AUC (from 5 minutes to 72 hours) from 8 to 24 hours is almost 6-fold than the AUC from 5 minutes to 6 hours. Therefore, both clearance and half-life will be affected if half-life and clearance are estimated from 5 minutes to 72 hours concentrations. Hence, a reliable and reasonable PK estimate should be obtained from baseline corrected concentrations which has been done in this report.

3. The disease state may have impact on the PK of rhAT III but from this study, it is difficult to conclude if indeed this is the case.

Study #3

Title: Population pharmacokinetic analysis and simulation of the plasma activity of recombinant human antithrombin (AT). Comparison to human plasma-derived antithrombin.

The objective of this investigation was to evaluate the pharmacokinetics of recombinant human antithrombin (rhAT) and human plasma derived antithrombin (hpAT) using population pharmacokinetic approach.

The pharmacokinetics of rhAT were evaluated in 15 patients with congenital antithrombin deficiency following a short intravenous infusion of 50 or 100 IU/kg. The data were obtained from the study AT III-009-00 (Study #2 in this review). The population pharmacokinetic parameters along with inter-individual variability are shown in the following Table 1.

Table 1
Population PK parameters of rhATIII in patients with congenital AT deficiency

Parameter	Value	Se[a]	CV(%)[b]	LLCI[c]	ULCI[d]
	Fixed effects				
Clearance; CL (L/h)	0.665	0.0493	7.41	0.56837	0.76163
Total distribution volume; Vss (L)	7.72	1.26	16.32	5.2504	10.1896
central distribution volume devisor (Vr) Vc = Vss/ (1 + Vr)	1.51	0.331	21.92	0.86124	2.15876
Inter-compartmental Clearance; Q (L/h)	0.613	0.0646	10.54	0.48639	0.73962
AT activity Baseline; BL (%)	50.7	1.16	2.29	48.4264	52.9736
	Random effects (inter-individual IIV)				
$\omega_{CL(IIV)}^2$	0.0676	0.0205	30.33	0.02742	0.10778
$\omega_{Vss(IIV)}^2$	0.0521	0.026	49.91	0.00114	0.10306
$\omega_{BL(IIV)}^2$	0.0083	0.0030	36.26	0.00241	0.01425
	Random effects (residual error)				
σ_1^2	0.00178	0.00021	11.91	0.00136	0.00220

[a] Standard error of parameter estimate

[b] Coefficient of variation

[c] Lower limit of 95% confidence interval

[d] Upper limit of 95% confidence interval

The clearance of rhAT was 0.665 liters/hr. From the POSTHOC estimation, the half-life and MRT of rhAT were 10.2 and 8.6 hours, respectively. The half-life of rhAT is comparable with the half-life observed in study AT III-009-00. The MRT is however, almost half than what was observed in study AT III-009-00. It is also surprising that the reported MRT by population approach is lower than the elimination half-life that is essentially in the opposite direction (in most of the cases). The method of calculation for MRT also does not appear in the

pharmacokinetic population model code therefore, it is difficult to assess the sponsor's method for MRT calculation.

To facilitate a comparison between the recombinant and human plasma derived products, the pharmacokinetics of hpAT were evaluated from a study performed in 1984 in the USA in 8 patients with congenital AT deficiency, following administration of a short intravenous infusion of 25 - 225 Units/kg hpAT. The population pharmacokinetic parameters along with inter-individual variability are shown in the following Table.

Table 2

Population PK parameters of plasma derived AT in patients with AT deficiency

Parameter	Value	Se[a]	CV(%)[b]	LLCI[c]	ULCI[d]
	Fixed effects				
Clearance; CL (L/h)	0.0910	0.0024	2.670	0.0862	0.0958
Total distribution volume; Vss (L)	9.820	0.601	6.120	8.642	10.998
Inter-compartmental Clearance; Q (L/h)	0.139	0.017	11.871	0.107	0.171
AT activity Baseline; BL (h)	44.9	1.65	3.675	41.7	48.1
	Random effects (inter-individual IIV)				
$\omega_{Vss(IIV)}^2$	0.0333	0.0116	34.834	0.0106	0.0560
$\omega_{BL(IIV)}^2$	0.0084	0.00694	82.619	-0.0052	0.0220
$\omega_{(\sigma_1^2)^2}^2$	0.295	0.137	46.441	0.0265	0.5635
	Residual error				
σ_1^2	0.00629	0.00245	38.951	0.0015	0.0111

[a] Standard error of parameter estimate

[b] Coefficient of variation

[c] Lower limit of 95% confidence interval

[d] Upper limit of 95% confidence interval

From the population analysis the values of clearance, half-life, and MRT were 0.091 liters/hr, 91.2 hrs, and 110.6 hrs, respectively. Plasma derived AT has almost a 9-fold longer half-life and 7-fold slower clearance than ATryn. The following Table summarizes the PK parameters of the two products.

TABLE 3

A PK comparison between ATryn and plasma derived AT

Parameters	rhAT	pdAT
CL (mL/hr/kg)	9.5	1.3
Half-life (hrs)	10.2	91.2
Vss (liters)	7.7	9.8

On the basis of pharmacokinetic population analysis and using Monte Carlo simulation, the optimal dosing regimen for rhAT in patients with congenital antithrombin deficient was selected. The dose selection was aimed at achieving an internal exposure to rhAT targeting plasma AT

activity to 80-120% of the level in normal subjects. According to this criterion, patients will receive a 15-minute loading infusion based on body weight and baseline plasma AT activity at the start of treatment. This is followed by a continuous infusion during the remaining time of treatment, again based on body weight and baseline plasma AT activity level.

The exposure and plasma AT activity during treatment with either rhAT or hpAT was determined by comparison of the simulated AT activity versus time profiles upon chronic administration in 100 patients of both products. For rhAT, the previously selected dosing schedule was used in the simulations. For hpAT, the dosing was selected from the package insert of hpAT. In 80% of the treated patients the plasma AT activity was between 80-120% of the mean population values in normal subjects (healthy subjects). Of the remaining patients, 6% has an activity lower than 80% while in 14% of patients AT activity was higher than 120%. In contrast, 41 % of the patients in the hpAT treated population had an activity within the 80-120% range at the 24 hour trough level (before infusion), while 23% patients were within the 80-120% range at the peak level (end of infusion, 15 minutes after trough).

Conclusions

Overall, the results of the study indicate that the PK of rhAT and hpAT are substantially different. The clearance of hpAT is lower (7 fold) than the clearance of rhAT and the half-life of hpAT is 10 times longer than the half-life of rhAT.

Study #4

Title: Population pharmacokinetic (PK) model for recombinant human antithrombin (rhA T): Validation on the results of study GTC AT III 01002.

The objective of the present study was to evaluate the predictive performance of the existing population PK model for recombinant human AT using AT activity data from a new safety and efficacy study performed in hereditary AT deficient patients undergoing high risk procedures such as surgery and childbirth (GTC AT III 01002).

The existing population PK model for AT is valid for the prediction of AT activity in non-delivery patients. In pregnant patients admitted for delivery, the existing model predicted higher levels of AT activity than actually observed. Both clearance and volume of distribution were higher in delivery than in non-delivery patients. By incorporating these PK differences and covariate Delivery (delivery or non-delivery), model's predictive power in pregnant patients was improved.

A Therapeutic Drug Monitoring (TDM) study was also conducted by administrating rhAT to AT-deficient patients undergoing surgery or child delivery. Using the algorithm for dosing of rhAT and previously developed population pharmacokinetic models, different scenarios of TDM were tested by simulating the effects of TDM on the plasma AT activity. Based on the data analysis it appears that the AT activity will be greater than 80% within 12 h of infusion for most (99.3%) of the patients. If the AT activity in a TDM sample is below 80% it is proposed to adjust the dosing rate with a factor of 1.3 times the current dosing rate. In case that the AT activity in a sample is greater than 120%, the dose rate should be reduced to 0.7 times the current dosing rate.

Comment

The analysis done by the sponsor is valid and can be used for the administration of rhAT to the AT-deficient patients as proposed by the sponsor. However, the AT model was generated using a small sample size (n =14) and as a result model's predictive power may not be as strong as the sponsor claims. This model however, may be of practical value and can be used to initiate a dosing scheme (rather than guessing the initial dose) to a given patient.